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Dated 22 September 2003

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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NP9 1RH

1. Your reference

REP07284GB

2. Patent application number
(The Patent Office will fill in this part)

09 JUL 2003

0316115.5

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Arachnova Therapeutics Ltd
95 Halkett Place
St. Helier
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08137770001

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

CHANNEL ISLANDS

4. Title of the invention

NEW THERAPEUTIC USE OF 4-(2-FLUOROPHENYL)-6-METHYL-2-(1-PIPERAZINYL)THIENO[2,3-D]PYRIMIDINE

5. Name of your agent *(if you have one)*

Gill Jennings & Every

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Broadgate House
7 Eldon Street
London
EC2M 7LH

Patents ADP number *(if you know it)*

745002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	6 ✓
Claim(s)	1 ✓
Abstract	
Drawing(s)	

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10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	NO

11. For the applicant
Gill Jennings & Every

I/We request the grant of a patent on the basis of this application.

Signature

Date
9 July 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

R E Perry
020 7377 1377

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Notes

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NEW THERAPEUTIC USE OF 4-(2-FLUOROPHENYL)-6-METHYL-2-(1-PIPERAZINYL)THIENO[2,3-D]PYRIMIDINE

Reference to Related Application

This Application is a continuation-in-part of PCT/GB02/02388, filed May 21, 2001.

Field of the Invention

This invention relates to a new therapeutic use for a known compound.

Background of the Invention

4-(2-Fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine monohydrate hydrochloride is known (see US-A-4695568) and has shown activity as an antidepressant. It has serotonin and noradrenergic reuptake-blocking properties and these may be the mechanism of its action as an antidepressant. The compound also has 5HT-3 blocking activity.

Pain can be characterised as mild, moderate or severe. It can be acute or chronic in nature. Acute pain tends to resolve within minutes or days but if it persists beyond two weeks or so it is often termed chronic. Pain can be due to trauma or inflammation, and this is often termed nociceptive pain. However, pain not simply due to these causes but due mainly to nerve dysfunction or dysfunctional processing of sensory impulses is often referred to as neuropathic or neurogenic pain.

Acute nociceptive pain is well managed with non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and aspirin if it is mild. For moderate pain, tramadol and codeine are useful. For severe pain, opiates such as morphine work well.

Mild to moderate chronic nociceptive pain due to inflammation is usually well managed with NSAIDs and COX-2 inhibitors although these drugs can cause serious gastric ulceration and bleeding. Tramadol is also very effective but can cause nausea, vomiting and constipation. For moderate nociceptive pain, opiates like oxycodone and codeine are useful but they cause constipation. For severe nociceptive pain, opiates such as morphine are the mainstay of treatment despite the risk of respiratory depression and addiction.

Fibromyalgia is a condition affecting 3-8 million people in the USA and approximately 80-90% of people affected are women. It is a chronic condition characterised by fatigue and widespread pain in muscles, ligaments and tendons.

Previously the condition was known by other names such as fibrositis, chronic muscle pain syndrome, psychogenic rhumatism and tension myalgia.

Few adequate treatments exist for neuropathic pain, and only gabapentin is licensed for this purpose. New medicines are urgently required for neuropathic pain. There is also a need for safer and stronger analgesics for nociceptive pain.

Functional bowel disorders are very common and include irritable bowel syndrome (IBS) and functional dyspepsia. IBS is the most common disorder diagnosed by gastroenterologists and one of the more common encountered in general practice. The overall prevalence rate is similar (approx 10%) in most industrialised countries. Some estimates of prevalence have reached 20%. The illness has a large economic impact on health care use and indirect costs, chiefly through absenteeism.

IBS falls into two categories of equal prevalence, constipation-predominant and diarrhoea-predominant. The available treatments are generally poor.

A recent approach to treating diarrhoea-predominant IBS has involved the use of alosetron. This drug works by blocking the 5HT-3 receptor. Other drugs with this mechanism of action have shown some limited activity in this disease, including granisetron. Alosetron, although effective, was withdrawn due to side-effects on the colon.

A recent approach to treating constipation-predominant IBS involved agonising the 5HT4 receptor. Two such agonists are in clinical trials, i.e. tegaserod and prucalopride. Other approaches being explored include using 5HT1 agonists such as buspirone.

Functional dyspepsia is characterised by impaired accommodation of the stomach to a meal and epigastric pain discomfort or pain. There is often early satiety and weight loss. The disorder is not well understood. Treatments include antispasmodics and drugs affecting gut motility. Early studies suggest that buspirone and serotonin reuptake inhibitors may be useful.

Summary of the Invention

Surprisingly, it has been found that the known compound identified above (referred to herein as MCI-225) has activity in the treatment of pain and related conditions having a pain component, e.g. functional bowel disorder and fibromyalgia. Its combination of serotonin and noradrenergic reuptake blockade and 5HT-3 receptor blockade has not

previously been identified as being responsible for activity in pain. It will be appreciated that any suitable form of the active principle may be used, e.g. another salt form, or a prodrug or active metabolite.

Description of the Invention

By means of this invention, pain can be treated, e.g. controlled or prevented. Further, fibromyalgin and functional bowel disorders and associated pain symptoms can be treated, e.g. controlled or prevented. Such disorders include irritable bowel syndrome, including diarrhoea-predominant, constipation-predominant, and alternating constipation/diarrhoea IBS. The patient may be male or female, diarrhoea-predominant IBS being particularly associated with women.

For use in the invention, the active compound can be formulated in any suitable manner together with a conventional diluent or carrier. The active compound is preferably administered by the oral route; other suitable routes of administration include sublingual/buccal, transdermal, intramuscular, intranasal, rectal, parenteral, subcutaneous, pulmonary and topical. An effective dose of the active agent will depend on the nature and degree of the complaint, the age and condition of the patient and other factors known to those skilled in the art. A typical daily dosage may be 0.1 mg to 1 or 5 mg.

A pharmaceutical composition containing the active ingredient may be in the form of a sublingual tablet or patch. Suitable compositions for oral use include tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups and elixirs. Suitable additives include sweetening agents, flavouring agents, colouring agents and preserving agents. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients, e.g. inert diluents such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated, to form osmotic therapeutic tablets for controlled release. Hard gelatin capsules may include an inert solid diluent, for example calcium

carbonate, calcium phosphate or kaolin; soft gelatin capsules may include water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

In the following studies, Study 1 shows the analgesic activity of MCI-225 at an oral dose of 30mg/kg, in an *in vivo* model of inflammatory pain. The effect was comparable to that of indomethacin (1mg/kg) , an NSAID widely used for chronic pain such as arthritic pain.

In Study 2, using intact animals, the ability of a drug to inhibit the reflex depressor response to colorectal distension can be assessed. In this model, an inhibition of the reflex indicates modulation of visceral nociceptive neurotransmission and, therefore, the use of the drug in functional bowel disease (e.g. IBS); see Kozlowski *et al*, 2000, Gut 46, 474-480. Allodynia and visceral pain are important components of functional bowel disease.

Study 1

Three groups of rats received vehicle, indomethacin or MCI-225. There were 13 rats in each group. Inflammatory pain was induced following a modified Randall Selitto method and the pain threshold of the inflamed paw was measured using a paw pressure analgesiometer. The threshold for paw withdrawal was measured in grams at 1 and 3 hours post dose. The results are shown in the following Tables.

Group	Treatment	Dose (mg/kg)	Group mean (± sd) pain threshold (g) of inflamed paw at:			
			1 hour pre-dose	2 hour pre-dose	1 hour post-dose	3 hour post-dose
1	Vehicle	0	191.5 ±88.56	146.5 ±28.82	135.0 ±36.23	135.0 ±34.10
2	MCI-225	30	147.7 ±65.91	138.5 ±34.72	170.8* ±39.47	205.4** ±68.30
3	Indomethacin	1	166.2 ±68.32	144.2 ±41.32	200.8* ±82.96	210.0* ±107.12

Group	Treatment	Dose (mg/kg)	Group mean changes (± sd) in pain threshold (g) from pre-dose reading at:	
			1 hour post-dose	3 hour post-dose
1	Vehicle	0	-11.5 ±50.56	-11.5 ±38.32
2	MCI-225	30	32.3* ±56.41	66.9** ±65.85
3	Indomethacin	1	56.5** ±56.18	65.8* ±95.17

sd = Standard deviation

Statistical significance of difference from vehicle-treated group: *$p<0.05$, **$p<0.01$

The results show that MCI-225 was able to increase the pain threshold by 32.3 g at 1 hour and 66.9 g at 3 hours. There is a statistically significant difference between these values and those for vehicle at the same time intervals. On this basis, MCI-225 is useful for the treatment of inflammatory and other pain.

Study 2

Experiments were performed on male Sprague-Dawley rats (250-300 g). Anaesthesia was induced with isoflurane (2.5% in oxygen) and maintained with alpha chlorolose (80 mg/kg i.v.). The left carotid artery was cannulated for the measurement of blood pressure and heart rate and the left jugular vein cannulated for drug administration. A tracheal cannula was implanted for artificial respiration if required. A 10 mm long latex balloon was inserted intrarectally so that the tip of the balloon was 20 mm from the anal verge (Kozlowski *et al*, *supra*). The balloon was connected via a double lumen cannula to a pressure transducer and also to a saline-filled syringe for inflation/deflation of the balloon. Throughout the experiment, body temperature was kept constant at 36-38 C using a homeothermic blanket.

Once stable baseline parameters were obtained (approximately after 20 minutes), the balloon was rapidly inflated with increasing volumes of saline (0.5-2.5 ml) for 30 seconds at 5 minute intervals, and the resultant change in blood pressure recorded. Three distinct response curves were constructed, with a 10 minute stabilisation period between each curve. In one group of animals, 10 minutes prior to the commencement of the final distension response curve, a single bolus of MCI-225 (3 mg/kg) was administered

intravenously; in a second group of animals, a single bolus dose of vehicle was administered. The effect of MCI-225 and vehicle was determined by analysing the changes in colorectal distension that evoked depressor response.

Falls in arterial blood pressure (mean absolute decreases in mean arterial pressure in mmHg, with standard error of mean in brackets) evoked by distension of the balloon, before adding drug, at 0.5, 1.0, 1.5, 2.0 and 2.5 ml balloon volume were 2.7 (1.9), 12.4 (5.9), 24.0 (8.9), 36.3 (4.8) and 43.4 (6.0), respectively (all except final value n=6, final value n=5). Following administration of MCI-225 at 3 mg/kg i.v., the corresponding values were 2.2 (1.65), 6.3 (2.6), 10.6 (3.9), 15.3 (5.4) and 24.6 (7.3), respectively (all values except final value n=6, final value n=5).

The results clearly show that MCI-225 inhibited the distension-induced falls in blood pressure. The falls in blood pressure evoked by 2.0 and 2.5 ml balloon volumes were reduced with statistical significance following administration of MCI-225 at 3mg/kg, with p values (paired t test) of less than 0.01 and less than 0.05 respectively.

CLAIMS

1. A method for the treatment of pain in a patient suffering therefrom, which comprises administering to the patient an effective amount of 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof.

2. The method according to claim 1, wherein the salt is the monohydrate hydrochloride.

3. The method according to claim 1, wherein the pain is nociceptive pain.

4. The method according to claim 1, wherein the pain is neuropathic pain.

5. A method for the treatment of a functional bowel disorder in a patient suffering therefrom, which comprises administering to the patient an effective amount of 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof.

6. The method according to claim 5, wherein the salt is the hydrochloride monohydrate.

7. The method according to claim 5, wherein the disorder is irritable bowel syndrome.

8. The method according to claim 7, wherein the disorder is diarrhoea-predominant irritable bowel syndrome.

9. The method according to claim 8, wherein the patient is female.

10. The method according to claim 7, wherein the disorder is alternating constipation/diarrhoea irritable bowel syndrome.

11. The method according to claim 7, wherein the disorder is constipation-predominant irritable bowel syndrome.

12. A method for the treatment of fibromyalgia in a patient suffering therefrom, which comprises administering to the patient an effective amount of 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof.

13. The method according to claim 12, wherein the salt is the monohydrate hydrochloride.